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A Unifying Framework for Understanding Biological Structures and Functions Across Levels of Biological Organization

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Synopsis The relationship between structure and function is a major constituent of the rules of life. Structures and functions occur across all levels of biological organization. Current efforts to integrate conceptual frameworks and approaches to address new and old questions promise to allow a more holistic and robust understanding of how different biological functions are achieved across levels of biological organization. Here, we provide unifying and generalizable definitions of both structure and function that can be applied across all levels of biological organization. However, we find differences in the nature of structures at the organismal level and below as compared to above the level of the organism. We term these *intrinsic* and *emergent* structures, respectively. Intrinsic structures are directly under selection, contributing to the overall performance (fitness) of the individual organism. Emergent structures involve interactions among aggregations of organisms and are not directly under selection. Given this distinction, we argue that while the functions of many intrinsic structures remain unknown, functions of emergent structures are the result of the aggregate of processes of individual organisms. We then provide a detailed and unified framework of the structure–function relationship for intrinsic structures to explore how their unknown functions can be defined. We provide examples of how these scalable definitions applied to intrinsic structures provide a framework to address questions on structure–function relationships that can be approached simultaneously from all subdisciplines of biology. We propose that this will produce a more holistic and robust understanding of how different biological functions are achieved across levels of biological organization.

Introduction

The structure–function relationship has been long studied and is of inherent interest to biologists working across levels from molecules to ecosystems. Scientists in many biological disciplines and related fields have collected enormous amounts of data about structure and function, but synthesis across these fields remains limited. To date, efforts have focused on syntheses across either higher or lower levels of biological organization (Nomura 2010; Farnsworth et. al. 2017; Leale et al. 2018; O'Connor et al. 2020), but not across all levels. Recent advances in technologies and institutional efforts to reintegrate biology will afford the necessary opportunities to integrate and analyze complex datasets.

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However, given the history of institutional silos organized around subdisciplines, common definitions and theoretical frameworks are needed that can be used across fields and levels of biological organization.

Structures and functions can be identified across all levels of biological organization. However, it is not clear whether the nature of their relationship is similar across levels. Yet, such an understanding is critical for current efforts to reintegrate biology. If the structure–function relationship is similar across levels of biological organization, researchers might be able to apply the same conceptual approaches to explore the nature of structures and functions. However, if the relationship is different across organization levels, we might discover new questions and gaps in knowledge that are specific to a subset of phenomena that occur at a subset of levels.

Our aim is to discover potential common features of the structure–function relationship that can be scaled across all levels of biological organization. First, we provide unifying definitions of structure and function that can be applied across levels. Second, we consider the degree to which the nature of the structure–function relationship is similar across levels of biological organization. Third, we propose that the nature of structures and functions are fundamentally different above and below organismal levels of organization. This is because structures at the organismal level and below are directly under selective pressures, contributing to the overall performance (fitness) of the individual organism, whereas structures and functions above this level (populations to ecosystems) are not.

An illustration of this distinction is that within the genome sequences of thousands of organisms that are now available, we often encounter coding potential for biological structures whose functions remain unknown. Similarly, we encounter subcellular structures whose function is not clear based on composition or morphology. This does not seem to be true at higher levels of biological organization. However, there may be concepts or approaches that span many, but not all levels, which could still enable valuable insights and discovery. Here, we explore these topics and offer a perspective about the scalability of the structure-function relationship that still allows for unifying concepts and approaches that can lead to a greater understanding of biological structures of unknown function.

What are structures and functions?

Despite—or because of—the broad usage of the terms structure and function across disciplines in biology, the definitions of structure and function vary. Here, we provide general definitions that transcend levels of organization and discipline. *Structure* is the arrangement of components that arise at or below the level of organization of the structure itself. Arrangements can include interactions or physical connections among components along with the positions in space that they occupy. Such arrangements pervade all units of biological organization, from molecules to ecosystems. *Function* is a transformation of structures, their components, matter, or energy that arises as a consequence of the physical characteristics of the structure—that is, function directly follows structure.

Does structure–function scale across levels of biological organization?

Structures are found at each level of biological organization (Fig. 1). Structures are generally organized in a nested hierarchy, aggregating with other structures to produce higher level structures. Starting at the lowest levels and moving up, we can see that atoms are arranged into molecules, molecules are arranged into organelles, organelles are arranged into cells, cells into tissues, and so on up to individual organisms (if they are multi-cellular). Continuing up, individuals are arranged into populations, populations are arranged into communities, and communities along with abiotic features of the environment, form ecosystems. Thus, it is straightforward to identify structures across levels of organization and to recognize that they occupy increasing spatial scales, from the primary structure of proteins to the age structure of populations and the network structure of communities.

There is at least one function that can be ascribed to structures at all levels of biological organization. These functions are a direct consequence the structure's physical characteristics. While function can influence structure, it does so indirectly through evolutionary processes. Hemoglobin, for example, has the function of binding oxygen, and it does so due to the specific arrangement of molecules in the protein. Differences in oxygen binding properties found in hemoglobin molecules from different species, or isoforms within a species, arose through adaptation. Likewise, the structure of an ecological network determines dynamic stability of population abundance in the community, and it does so via the type and strength of interactions connecting different populations within the community (Thébault and Fontaine 2010; Guimarães 2020; Landi et al. 2018). Thus, structures and functions can be found at all levels of organization, as can a link between the function and the structure itself.

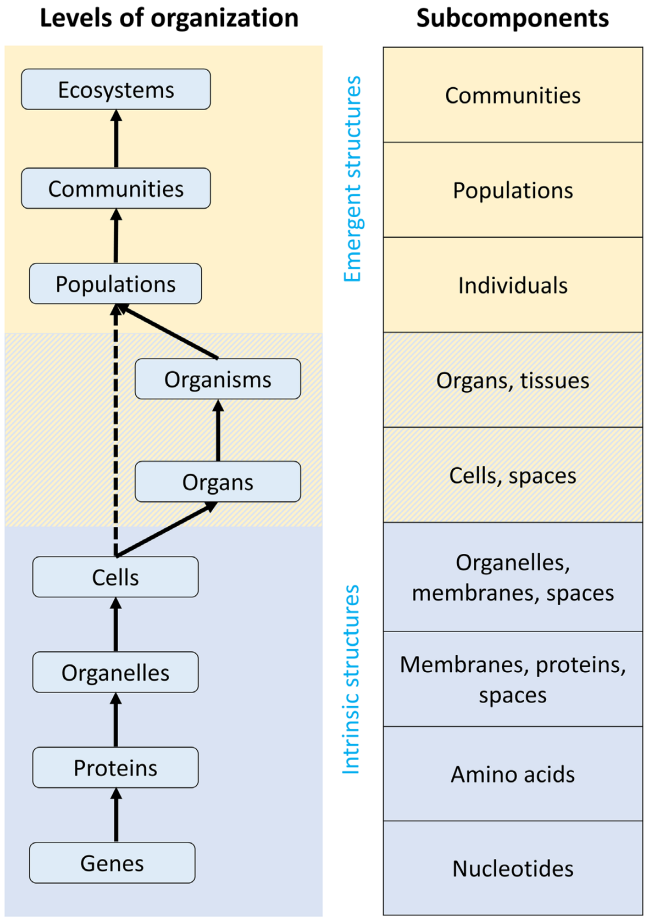

Fig. 1 Levels of biological organization from genes to ecosystems. Structure can be identified at each level of organization, often in the way that entities from the level below are arranged and nested within the focal level. For example, organelles are nested into cells, and the arrangement of organelles is part of the cell's structure. Structure, however, includes more than just being nested, as particular arrangements in space, along with additional components such as abiotic features of the environment in ecosystems or interstitial fluids in organisms, add to structure. Note, the major evolutionary transition from unicellular to multicellular individuals created new levels of organization for metazoans, such as organs, that do not occur in unicellular organisms (marked with the blue/yellow striping). Thus, emergent structures begin above the level of the cell for bacteria, protozoans, and yeast, and above the organism in metazoans.

However, the nature of structure and function are fundamentally different between the level of organization from the organism down and the levels above the organism. We will call these intrinsic and emergent structures, respectively. This is primarily because structures at the level of the organism down have functions that directly impact the overall performance (fitness) of the individual organism. Furthermore, intrinsic structures arise from development and can be physically identified at most levels. For example, cells are composed of organelles (level below); and overall protein structure is dependent on the domains contained within that protein (same level). Above the level of the individual, structures arise out of the interactions among organisms without being part of a unit of selection. They are still arrangements of components that generally arise at or below the level of organization of the structure itself. At these levels, arrangements can include interactions (e.g., trophic or non-trophic) and positions in space but do not need to be in physical contact. At the level of populations, structures are distributions of individuals of different types (e.g., age, class and social) as well as among-individual interactions including mating, competition, or cannibalism. At the level of communities, structures are distributions of species and their interactions, including predator–prey, mutualism, or competition, while at ecosystem level, structures are the interactions among organisms and between them and their abiotic environment. Thus, structures continue to occur at higher levels of organization, but they are generated across larger spatial and temporal scales. However, the relation of these structures to function is different. For example, the age structure of a population affects the function of population growth, but population growth is an emergent outcome of this structure. Age structure

was not generated during the course of individual growth and development, it is a characteristic of the aggregation. Furthermore, the age, stage, genetic, and social structures of populations, and the trophic and mutualistic network structures of communities are all strongly determined by the dynamics driven by the function itself. Trophic structure influences food web stability, influencing the abundance and structure of populations, which further alters food web structure. Structure, function, and dynamics are part of a never-ending feedback cycle above individuals, but from individual organisms on down, structures are developmental outcomes.

Thus, while we recognize structures and functions across levels of biological organization, the relationship between structure and function at the organismal level and below is different from that above. This is because at the organismal and sub-organismal levels, the structure–function relationship is defined and constrained by fitness, while above it is not. Indeed, structures at the level of individual and below are developmental and thus are both inherited and subject to phenotypic plasticity. This implies that evolutionary history may inform comparisons of structures across species and allow for the prediction of the function of many structures. In contrast, no aspect of structure above individuals is inherited, and the function of structure at these levels is simply the aggregate rates of reproduction, metabolism, nutrient turnover, or decomposition. Furthermore, it is clear that selection acting directly on intrinsic structures can have consequences for emergent structures. However, selection does not act directly on emergent structures. Above the level of individual organisms, the challenge is to predict the magnitudes, directions, and rates of known processes, whereas at the level of organisms and below, the challenge is often to simply identify the function at all. Thus, we often encounter intrinsic structures of unknown function, but that is not the case for emergent structures. For these reasons, we delve further into the nature of structure and the structure-function link at the level of organisms and below.

Expanded concept of intrinsic biological structure and function

Inherent to intrinsic biological structure is three-dimensional shape, organization, and patterning. However, the composition of intrinsic structures varies at each sub-organismal level, sometimes being an arrangement of structures from the level below, but also composed of fragments at the same level that are in physical contact (Fig. 1). For example, proteins are composed of the atoms that make up amino acids (level below) and the arrangement of peptides that fold into distinct shapes. Despite this, an expanded concept of intrinsic structure will help map a given structure to one or more functions and link the functional consequences of a given structure across sub-organismal levels. For example, the functions of mitochondrial integral membrane proteins have consequences for mitochondrial function, which could impact cellular functions, such as respiration. We suggest that a given intrinsic structure at any level can be broken down to two major components: a central core that provides a foundation and a region of increasing variability that allows for adjustment and ultimately further adaptation (Fig. 2).

The function of a given intrinsic structure is defined as its role within a larger assembly or level of biological organization that is also dependent on the context (physiological or environmental state), its own inherent dynamics (time-dependent motion), as well as its interaction with other structures within and across biological levels. Examples of intrinsic structure function are molecular interactions (e.g., binding), product production, or synthesis of building blocks for larger structures, such as membrane structures within organelles. For example, gene expression, which can be regulated by cell signaling networks, directs the assemblage of molecules. The collection of expressed gene products can be involved in the specification of cell fates that dictate cell functions. Subsequently, the accumulation of cells forms tissues, and the accumulation of tissues can constitute various functional components of an organ. An organ will ultimately produce function(s) at the organismal level, which is necessary for the survival of that organism within its environment. Dynamic feedback between the levels ensures a robust function of structures with increasing complexity. Therefore, over evolutionary time scales, reciprocal interactions across levels, including above the organismal level, drives the evolution of form and function across these same scales. What principles direct these multidimensional structure–function relationships, how physiological state and variable interactions impact that relationship, and how structure–function relationships scale across sub-organismal levels of biological organization remains an open question. We suggest these level-independent definitions are the first step in creating a unified concept.

Core

At the innermost level of a given sub-organismal structure, there is commonly a central core that serves as a foundation (Fig. 2). Core is a common term in protein (Kuhlman and Bradley 2019), genome (Wang et al. 2021), and biological networks (Barabási and

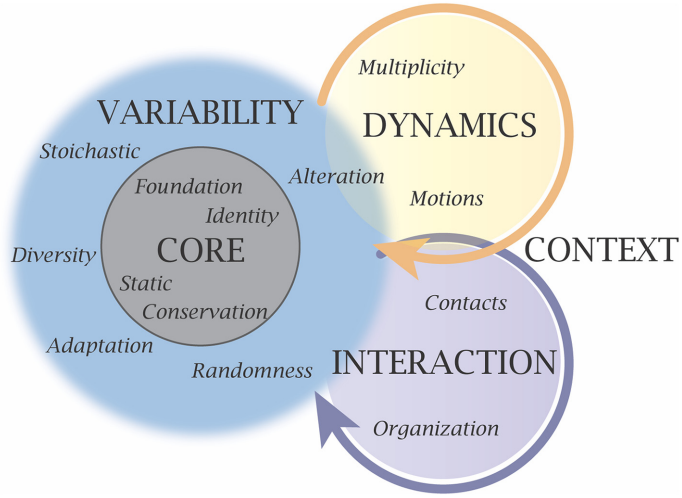

Fig. 2 Intrinsic biological structures can be characterized by core and variability shells of organization and are used to predict function. Dynamics and extrinsic interactions extend the functions of intrinsic biological structures providing a larger context for biological function.

Oltvai 2004), but also extends to other disciplines including material science (Ha and Lu 2020), architecture (Trabucco 2008), and business systems (MacCormack 2010), making it a guiding principle. The nucleus of a eukaryotic cell is a common example of a biological core. The core will also be the region of a structure most resistant to change. Thus, the core allows for broad scale comparisons of structure–function relationships amongst the most diverse biological entities, but the core alone may be insufficient to predict function.

Variability

A continuum of variability surrounds the core for any given structure (Fig. 2). The variable region of a structure is influenced by functional requirements that can affect the shape or aggregate of the composite structure. The variable region allows for a plastic response to conditions and can evolve more rapidly than the core. Thus, the variable region can be used to directly compare organizational components within lineages but could be less useful for comparisons across diverse entities as changes may have evolved significantly.

The variable region of a structure is more diverse, making it more able to accommodate adaptive changes than the core and contains a spectrum of strong to weak sequence homologies that imparts structural adaptations to modulate function. These regions are strongly influenced through direct or even stochastic interactions with other structures to promote coevolution. The accumulation of additional structure or domains in this region can vastly expand or even restrict activities of the core. The greatest structural divergence within the variability region comes from biological entities that are not under biochemical, phenotypic, or fitness constraints (Cooper and Brown 2008). This allows for the accumulation of rapid and broad alterations while not disrupting other functional requirements of the organism. Ultimately, this will allow for rapid evolution and accumulation of new adaptive functions within the variability level that may end up funneling towards a new core structure.

An example of core and variability at the subcellular level of biological organization

Comparative genomics evaluates the similarities of genomes across a large diversity of organisms to better understand features of evolution. In this example, the structure is the genome or individual gene sequences. Highly homologous genetic sequences would better predict essential genes and functions or stable regions within the genome (even in diverse organisms). These orthologous genes generally have a common ancestral origin, are little changed by speciation, and would therefore represent the core. There are even highly conserved sub-sequences within genes that generally represent active sites and that are required for the protein core structure or indicate sites of interactions. As a result, the associated protein structures and functions are more likely to be retained across species, and the comparison of ortholog-derived genes could provide greater insights into function (Bergmiller Ackermann and Silander 2012; Gabaldón and Koonin 2013).

Degrees of variability are represented by the more divergent or entirely novel genomic sequences within or between organisms. As an example, paralogs are commonly derived from gene duplications and are ultimately less constrained and can evolve through the

acquisition of specific mutations that impart new adaptive functions and fitness (Orr 2009) while still retaining the central core sequence and structure (Koonin and Galperin 2003). The best-known example of paralogs includes the vertebrate Homeobox (Hox) genes, which resulted not only from individual gene duplications but also from whole genome duplications resulting in 39 genes arranged on four chromosomes (Pineault and Wellik 2014). This rapid expansion and evolution of Hox genes resulted in collinear and overlapping input on embryonic vertebrate limb development and ultimately function. Other common examples of gene paralogs include the globin genes that carry oxygen and the RNase A superfamily which contains both Angiogenin and RibonucleaseA. These paralogs retained a core of common protein structure but contain sufficient variability to evolve entirely divergent functions. Ultimately, new activities and functionalities can be gained through a limited number of catalytic site mutations while at the same time retaining the core (Ribeiro et al. 2020). Therefore, paralogs are under reduced or different evolutionary constraints with respect to the gene from which they are derived and have more freedom to evolve new functions or coevolve separately to influence novel functions.

An example of core and variability at the organismal level

The concepts of core and variable regions can also be applied to structures at other levels of biological organization. We can use a given appendage, like the pectoral fin of ray-finned fishes, as an example. The core of the distal pectoral fin structure is its common set of elements, the lepidotrichia, or fin rays. However, across species, the variable region of the structure—the size, shape, and arrangement of these core elements—can change, and greatly impact function. For example, wrasses are a highly diverse family of coral reef fish that primarily rely on the pectoral fin for propulsion (labriform swimming; Walker and Westneat 2000, 2002a, 2002b). Across species of wrasses a continuum of labriform swimming behavior exists that ranges from rowing to flapping. Rowing species perform drag-based propulsion for high maneuverability while flapping species perform lift-based propulsion that maximizes mechanical efficiency (Walker and Westneat 2000, 2002a, 2002b). The continuum of swimming behavior is directly associated with interspecific differences in fin ray morphology (Aiello et al. 2018a, 2018b). Rowers use relatively flexible broad (paddle-like) fins while flappers use stiff wing-like fins (Walker and Westneat 2000, 2002a, 2002b; Wainwright et al. 2002; Aiello et al. 2018a, 2018b). The fin rays of rowers are relatively unbranched and of a lower radius of the second moment of area, providing more flexibility than flappers (Aiello et al. 2018a, 2018b). In comparison, the fin rays of flappers are highly branched and of a greater radius of second moment of area (Aiello et al. 2018a, 2018b). Thus, interspecific differences in swimming behavior are paralleled by interspecific differences in fin shape, fin ray branching pattern, and fin ray geometry, providing some variability to the core.

Dynamics and interactions

The dynamics and component interactions are critical structural properties required to produce robust functional outputs (Fig. 2). *Dynamics* is the time and space-dependent motion of a structure and its subcomponents. *Interactions* are the direct or indirect time-varying connections between different biological entities, and thus often occur through structural dynamics.

At sub-organismal levels of organization, the function of a given structure can depend on its dynamics and interactions with other structures. Therefore, functional differences of two similar structures can occur through differences in dynamics and interactions with other structures. For example, at the molecular level, motor protein kinesins use variation in the mobility of the peripheral region surrounding the ATP-binding pocket to alter the mechanochemical cycle (Hwang et al. 2017). Further, the exquisite sensitivity of the $\alpha\beta$T-cell receptor in antigen discrimination requires mechanical force that influences the domain motion of the receptor, thereby controlling the binding strength (Hwang et al. 2020). Similarly, at the organismal level, the functional capabilities of a locomotor appendage depend as much on its morphology (size, shape, and mechanics) as its movement, and interspecific differences in locomotor performance can arise through evolutionary changes to both the morphology and movement of locomotor appendages (Aiello et al. 2020). In these cases, functional differences between structures occur through differences in both structures and dynamics rather than solely through discrete changes in structure.

An example of dynamics and interactions at the cellular and subcellular levels

The intricate process of gene regulation involves multiple factors coordinated in a spatiotemporal manner by positive/negative feedback and feedforward loops (Alon 2007; Davidson and Levine 2008; El-Sherif and Levine 2016; Peter and Davidson 2017). For example, the formation of dorsal appendages (DAs) on the *Drosophila* eggshell is regulated by the epidermal growth factor receptor (EGFR) activation in the layer

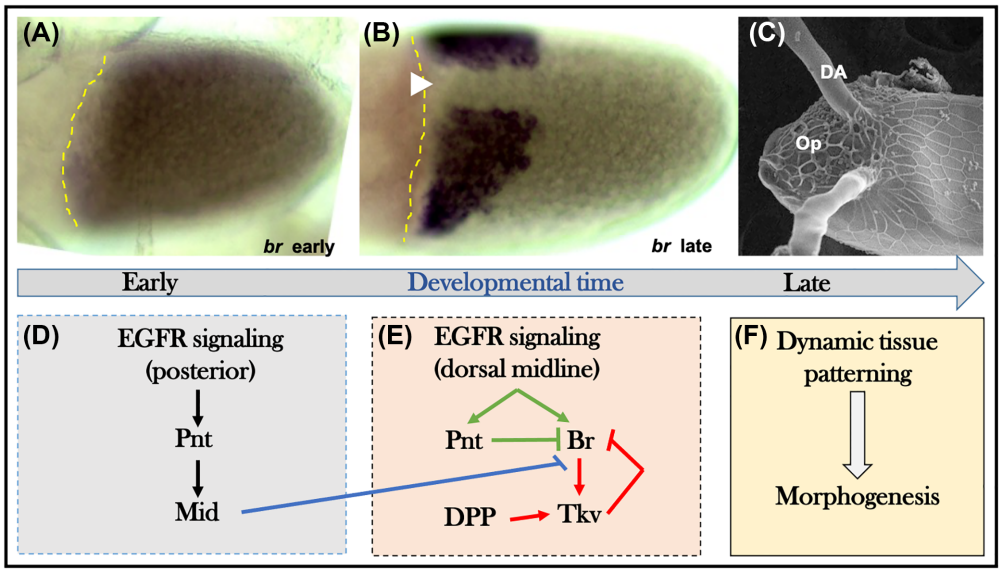

Fig. 3 Spatiotemporal dynamic patterning of the 2D follicle cells (FCs) form the three 3D structures of the eggshell. *In situ* hybridization of **(A)** Early uniform *br* expression in the FCs of the *Drosophila* egg chamber. **(B)** Late *br* expression in the FCs. The anterior border of the FCs is marked by a yellow broken line. The dorsal-midline is denoted by a white arrowhead. **(C)** *D. melanogaster* eggshell. Dorsal appendage (DA) and operculum (OP) are denoted. Anterior is to the left in all images. (**D and E**) Transcriptional networks controlling the patterning of early and late *br* expression. The blue repressing arrow between D and E marks the memory generated by the early EGFR signaling that restricts the late *br* pattern. The feedforward (green arrows) and negative feedback (red arrows) regulatory loops mark the expression and repression of late *br*. **(F)** Diagram of the general concept.

of follicular epithelium engulfing the growing oocyte (Berg 2005; Revaitis et al. 2020). The DAs primordia are formed by a feedforward loop comprised of the Zinc-finger transcription factor *broad* (*br*), which is split in the middle by the ETS-transcription factor Pointed (PNT); both are regulated by EGFR activation (Fig. 3; Boisclair-Lachance et al. 2009; Zartman et al. 2009; Pyrowolakis et al. 2017). The pattern of *br* is turned off by the activation of the bone morphogenetic protein signaling via a negative feedback (Deng and Bownes 1997; Yakoby et al. 2008; Fuchs et al. 2012; Cheung et al. 2013; Marmion et al. 2013). In addition, the posterior boundary of *br* is set by Midline (MID) and PNT that are induced by an earlier posterior activation of EGFR (Fig. 3D and E; Fregoso Lomas et al. 2016; Stevens et al. 2020). Hence, a feedforward followed by a negative feedback controls morphogenesis (Fig. 3F).

Selective pressures on intrinsic structures are influenced by emergent structure interactions

While intrinsic structures are confined to sub-organismal levels of biological organization, interactions between biological entities can and do occur across levels of biological organization, and the structure–function relationship at one level of organization often impacts those at other levels. We argue that interactions that begin at sub-organismal levels can ultimately impact species interactions at the levels above the organism, and that interactions at the higher levels are ultimately driving changes at the lower levels through evolutionary processes. In sum, reciprocal interactions along both directions along the molecule–ecosystem continuum drive the evolution of structural interactions and their functional output.

Integrative example spanning levels from subcellular to ecosystems

The predator–prey evolutionary arms race is an example of a reciprocal interaction driving evolutionary change across levels. Most animals have multiple predators that need to be evaded in order to increase their chances of survival, and ultimately, fitness. In many species, predator avoidance occurs through a quick and agile escape response that accelerates the animal away from a threat, and a successful escape is often dependent on the maneuverability, speed, or force production of a prey species (e.g., Srygley and Dudley 1993). Using an ecological selective pressure for increasing the locomotor speed of a prey animal as an example, it is possible to identify how species-interactions can drive the evolution of subcellular processes and interactions in a single species.

One means to increase the distance traveled per locomotor cycle is to increase the force produced

during each cycle. Animal movement arises through the interaction of multiple integrated physiological systems with the physical environment (Dickinson et al. 2000). In many animals, muscles are the primary producer of force, and muscle itself is a composite and hierarchical structure composed of many repeated subcomponents (Josephson 1985; Maughan and Vigoreaux 1999; McCulloch 2016). At the level of the sarcomere, the repeating subcellular unit, are the actin and myosin proteins, which are the primary drivers of muscle contraction and, thus, force production (Josephson 1985; Maughan and Vigoreaux 1999). The arrangement and isoforms of these contractile units are under strong selective pressures, which lead to interspecific differences across muscles (Tune et al. 2020).

Changes in the protein isoforms or to the spatial arrangement of the actin and myosin proteins (e.g., nanometer scale differences in the spacing between adjacent actin and myosin filaments) can translate to differences in whole muscle function (Tune et al. 2020). Therefore, selective pressures at the ecological level can drive the evolution of subcellular protein arrangements that in turn can impact whole muscle function, or in the case of the outlined predator–prey example, muscle force production and the ability to evade predation. While the ability to better avoid predation through greater muscle force production is just one of the many ways selection acts to increase the fitness of the prey (e.g., act on the nervous system to increase reaction time), any ability to better evade predators then puts a selective pressure on the predator to increase its capture ability. In sum, reciprocal interactions along both directions of a molecule to ecosystem continuum drive the evolution of structures, interactions between multiple subcomponents, and ultimately, their functional output.

Conclusion and final remarks

Structure and function are foundational concepts that span all of biology. One can derive definitions, as we have done, that hold across all levels of biological organization: *structure* is an arrangement of components and *function* is transformation of components or resources. We have also shown that structure can represent more abstract or non-geometric features such as genomic organization, cell signaling networks, age distribution, or community-level interaction networks. If a given arrangement of components can be represented in a suitable space of descriptors, it is possible to treat abstract relations as structures and map the corresponding functions. However, on closer examination, we find that while structures and functions are found at all levels of biological organization, the relationship between structure and function is not entirely the same across that organization. This seems surprising at first glance. However, the reason for the difference is not surprising: evolution and natural selection permeate biological systems and impact fitness at the level of the organism, whereas above the organismal level they do not.

Given this framework of the structure–function relationship, how do we reintegrate biology? The suggestion that a given structure can belong to one of two categories warrants careful examination to understand and describe the differences in order to reintegrate biology. At the organism and sub-organism levels, structure arises from developmental processes and contributes to organismal fitness; we name these *intrinsic structures*. Above the organismal level, structures emerge from the interactions among organisms and abiotic components of the ecosystem and are not subject to selection; we name these *emergent structures*. This realization helps to understand that the existence of structures (genes, proteins, and novel tissues or even appendages, etc.) with unknown functions is a unique feature of intrinsic structures. A way forward is to identify fundamental concepts that may serve as guides for elucidating the structure–function relationship of intrinsic structures in a broad range of biological systems. These concepts—core, variability, dynamics, and interactions—will allow for insights that can reintegrate across the applicable levels of organization. In addition, while we can recognize core, variability, dynamics, and interactions across all levels of biology, understanding how they are applied to intrinsic versus emergent structures will allow for greater understanding of biological functions critical for a true reintegration of biology.

Data availability

No original data collection or analysis was used to formulate the conclusions of this manuscript.

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